JOC*Note*

Improved Julia−Kocienski Conditions for the Methylenation of Aldehydes and Ketones

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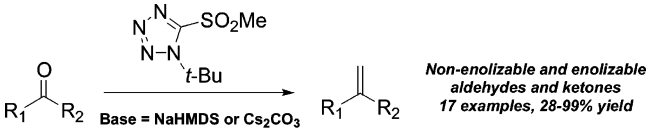


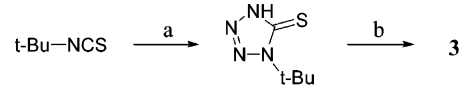
The scope of the methylenation of aldehydes and ketones under optimized Julia−Kocienski conditions is broadened by using 1-*tert*-butyl-1*H*-tetrazol-5-ylmethyl sulfone. Two different Barbier-type procedures are applied with NaHMDS at −78 °C or Cs_2CO_3 at 70 °C. The latter conditions are also adapted for the preparation of 1,2-disubstituted olefins and intramolecular olefination reactions.

Terminal olefins have received particular interest among alkenes, and methods ranging from anionic reactions developed by Wittig,[1] Johnson,[2] and Peterson[3] to other stoichiometric methods based on gem-dimetallic reagents have been reported.[4] A rhodium-catalyzed methylenation of aldehydes also has been developed recently.[5] The Julia−Kocienski reaction is a very efficient method to transform carbonyl compounds into olefins, as illustrated by the recent total synthesis of the triester of Viridiofungin A, A2, and A4[6] among others.[7] Surprisingly, the methylenation of carbonyl compounds under Julia−Kocienski conditions has been studied only briefly by Julia and co-workers with the benzothiazol-2-ylmethyl sulfone **1**[8] (Scheme 1) and more recently by Nájera's group.[9] Additionally, phenyltetrazolylmethyl sulfone **2** has been used in the formal total synthesis of (−)-agelastatin A.[10] Motivated by our general interest for this reaction, we embarked on a more comprehensive study of the methylenation of ketones and aldehydes under modified Julia−Kocienski conditions.

SCHEME 1

1 (BT) **2**, R = Ph (PT) **3**, R = *t*-Bu (TBT)

SCHEME 2. Synthesis of 3[a]



4

[a] Reagents and conditions: (a) NaN_3, *i*-PrOH/H_2O, reflux, 77%. (b) (1) NaH, MeI, THF; (2) $Mo_7O_{24}(NH_4)_6$, H_2O_2, EtOH, 91%.

Kocienski isolated products of the intermolecular *ipso* nucleophilic attack of α-lithiated BT-alkyl sulfones onto the heteroaryl moiety.[11] It is reasonable to assume that a BT-methyl sulfone like **1** has an even stronger reactivity in this degradative pathway, as the steric hindrance around the carbon atom attached to sulfur atom is reduced. Furthermore, Kocienski demonstrated also that TBT-alkyl sulfones are more stable to this autocondensation reaction than their PT or BT counterparts. We chose in consequence to prepare the sulfone **3** for our work. This was realized in a classical fashion on a 10 g scale in 91% yield from the mercaptan **4**[12] in two steps by alkylation and subsequent oxidation (Scheme 2).

It became rapidly clear that a Barbier-type procedure was convenient, the generation of the premetalate of the sulfone leading only to low conversion to the terminal alkene and important degradation. Two different sets of conditions have emerged from the initial optimization study. With conditions A, NaHMDS was used as a base in THF at low temperature. With conditions B, Cs_2CO_3 was used in a THF/DMF mixture at reflux. The use of Cs_2CO_3 is precedented for a Julia−Kocienski olefination reaction, but on activated methylene substrates.[13] Other inorganic bases were totally inefficient, except for K_3PO_4, which however remained inferior. Under those second conditions (B), the choice of solvent is also important. DMF must be present and is superior to other polar cosolvents such as MeCN.

The scope of the reaction appears in Table 1. Aldehydes and ketones reacted smoothly to furnish the desired terminal olefins in good to excellent isolated yields. The reaction displayed a good functional group compatibility as esters, lactones, carbamates, acetals, silyl, and *p*-methoxybenzyl ethers were tolerated. Moreover, aromatic and aliphatic substrates are equally

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(8) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett*. **1991**, *32*, 1175−1178.
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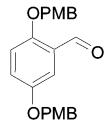
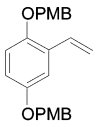
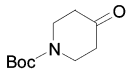
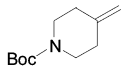
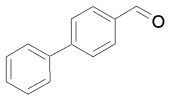
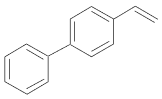
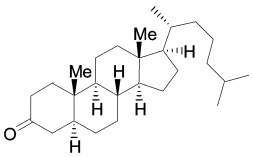
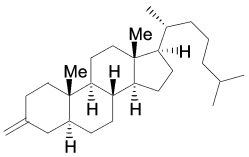
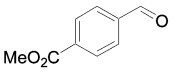
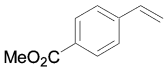
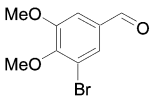
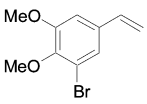
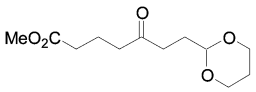
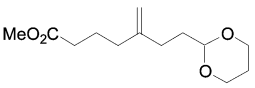
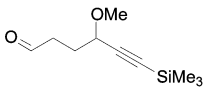
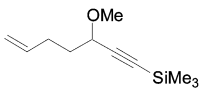
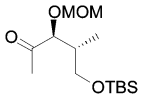
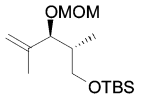
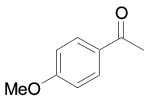
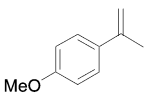
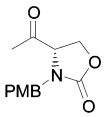
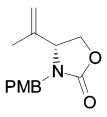
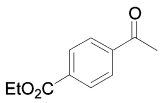
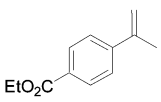
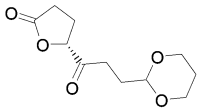
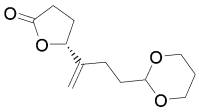
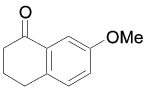
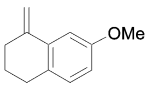
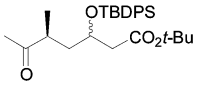
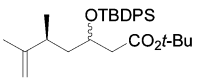
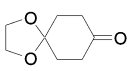
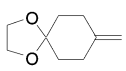
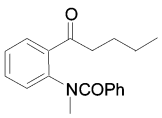
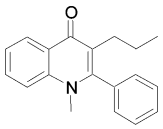
TABLE 1. Formation of Terminal Olefins[a]

aldehyde/ketone	olefin	Protocol, Yield%	aldehyde/ketone	olefin	Protocol, Yield%
 **5**	 **25**	A, 93	 **14**	 **34**	A, 92 B, 93
 **6**	 **26**	B, 93	 **15**	 **35**	A, 76
 **7**	 **27**	B, 80	 **16**	 **36**	B, 57
 **8**	 **28**	B, 92	 **17**	 **37**	A, 99
 **9**	 **29**	B, 96	 **18**	 **38**	A, 77
 **10**	 **30**	A, 77 B, 63	 **19**	 **39**	A, 85
 **11**	 **31**	B, 71	 **20**	 **40**	A, 59 B, 93
 **12**	 **32**	B, 45	 **21**	 **41**	A, 90
 **13**	 **33**	A, 90 B, 84	 **22**	 **42**	A, 71

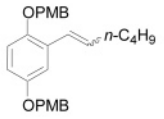
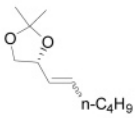
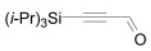
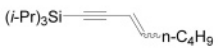
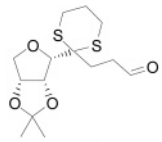
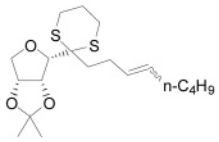
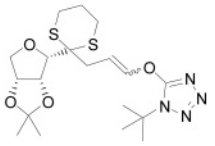
[a] Isolated yields. PMB: *p*-methoxybenzyl. TBSO: *tert*-butyldimethylsilyloxy. OTBDPS: *tert*-butyldiphenylsilyloxy. For compounds **38**−**40**, enantiomeric excess was determined by chiral GC.

good candidates for the transformation. Concerning the aromatic substrates, both electron-rich and electron-poor carbonyl compounds reacted well, as illustrated by aldehydes **5**−**8** and ketones **10** and **11**. Notably, both conditions A and B compared favorably with the original Julia procedure for the conversion of **10** to **30**. Conditions B gave 2-adamantene **36** in 57% yield, which compared well with the same transformation obtained with Wittig[14] or Peterson[15] procedures. Enolizable substrates such as **9**−**20** were also completely converted. As illustrated with compounds **38**−**40**, conditions A did not induce epimer-

(14) (a) Hughes, L.; Ingold, K. U.; Walton, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 7494−7499. (b) Bishop, R.; Gum Hee, L. *Aust. J. Chem.* **1987**, *40*, 249−255.

(15) Sekiguchi, A.; Ando, W. *J. Org. Chem.* **1979**, *44*, 413−415.

TABLE 2. Formation of 1,2-Disubstituted Olefins

aldehyde/ketone	olefin	Yield%(*E*/*Z*)[a,b]
		98(4/1)
5	**46**	
		60(7/3)
43	**47**	
		72(4/1)[c]
44	**48**	
		48(3/1)
45	**49**	
		6(1/2)
	50	

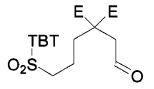
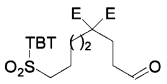
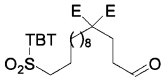
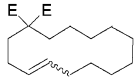
[a] Conditions B were applied with *n*-$C_5H_{11}SO_2$TBT **51** instead of **3**. [b] *E*/*Z* ratio was determined by NMR. [c] Conditions B but at room temperature.

ization of stereocenters. Enantiomeric excesses of ketones **18** (99%),[16] **19** (84%),[17] and **20** (94%)[18] were not altered in the terminal alkenes **38** (99%), **39** (85%), and **40** (97%), respectively. More drastic conditions B tested on **20** showed in contrast a loss of enantiomeric purity for **40** from 94% to 61%. Finally, intramolecular condensation occurred with **23** to give **43**.

We then explored the possibility of preparing other classes of alkenes under conditions B (see Table 2). Aliphatic, aromatic, and propargylic aldehydes reacted well with *n*-pentyl-TBT-sulfone **51**,[11] giving good to excellent yields of the expected 1,2-disubstituted alkene products. The functional group tolerance of the reaction was preserved and the stereoselectivity was similar to what is generally observed for TBT-alkyl sulfones. The more reactive propargylic aldehyde **44** led to completion even at room temperature. With aldehyde **45**, the yield of isolated olefin **49** dropped to 48%, accompanied by 6% of **50**. We assume **50** results from the condensation of the enolate formed from **45** onto sulfone **51**. Moreover, limitations also appeared when the preparation of 1,1′,2-trisubstituted olefins was attempted, the conversions remaining below 30%.

Finally we thought that those Barbier-type procedures could be adapted to intramolecular reactions. To the best of our knowledge, besides a few examples of intramolecular Julia aldol condensation,[19] only one failed attempt of intramolecular olefination under the modified Julia−Kocienski conditions has been reported during the total synthesis of rhizoxin D.[20] Conditions A were discarded rapidly, as they led to decomposition of the tested substrates. In contrast, conditions B were well suited, as shown in Table 3. The substrates **52**−**54** were added over 15 h via syringe pump onto a suspension of Cs_2CO_3 in refluxing THF/DMF. Cyclohexene **55** could be formed in 91% yield. Medium and large rings **56** and **57** were obtained in more modest yield, reflecting the inherent difficulty to form such rings when no beneficial conformation effect is implemented in the precursors. For these substrates, best results were obtained by replacing THF with 1,4-dioxane and heating the suspension to 100°C.

TABLE 3. Intramolecular Olefination

Precursor	Cycloalkene	Yield%(*E*/*Z*)
		91
52	**55**	
		32 (1/1)[a,b]
53	**56**	
		56 (2/1)[a,b]
54	**57**	

[a] THF was replaced by dioxane. [b] *E*/*Z* ratio was determined by NMR.

In summary, we have developed two very efficient, simple, and general procedures for the preparation of terminal olefins from both nonenolizable and enolizable aldehydes and ketones, that show a broad functional group tolerance.

Experimental Section

Representative Procedure for Conditions A: 1,4-Bis-(4-methoxybenzyloxy)-2-vinylbenzene (25). At −78 °C, NaHMDS (119 mg, 1.3 equiv) was added as dried solid in one portion to a solution of aldehyde **5** (189 mg, 1 equiv) and sulfone **3** (123 mg, 1.2 equiv) in THF (5 mL) under argon. The mixture was stirred for 16 h, maintaining the flask dipped in the dry ice bath with warming slowly to room temperature. The reaction was quenched by adding a saturated solution of NH_4Cl. After extractions with MTBE, the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexanes/AcOEt: 7/1) gave **25** as white solid (175 mg, 93%

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yield). Mp 92−95 °C. IR (film) 3048, 1612, 1249, 918, 824 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (2H, d, $J = 8.9$ Hz), 7.36 (2H, d, $J = 8.7$ Hz), 7.15 (1H, d, $J = 2.7$ Hz), 7.09 (1H, dd, $J = 18.1$ Hz, 11.2 Hz), 6.93 (2H, d, $J = 8.7$ Hz), 6.92 (2H, d, $J = 8.7$ Hz), 6.89−6.81 (2H, m), 5.73 (1H, dd, $J = 17.7$ Hz, 1.2 Hz), 5.26 (1H, dd, $J = 11.5$ Hz, 1.2 Hz), 4.97 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 159.4, 153.3, 150.6, 131.6, 129.5 (2C), 129.4 (2C), 129.2 (2C), 128.3 (2C), 115.0, 114.7, 114.4, 114.1 (2C), 114.0 (2C), 113.0, 71.3, 70.6, 55.4. MS (EI) *m*/*z* (rel intensity) 376 (2), 121 (100), 91 (2). HRMS (EI) *m*/*z* 376.167947 $(M)^+$, calcd for $C_{24}H_{24}O_4$: 376.167460. Elemental Anal. C 76.51; H 6.36. Calcd: C 76.57; H 6.43.

Representative Procedure for Conditions B: 4-Vinylbiphenyl (26). A suspension of Cs_2CO_3 (5.36 g, 3 equiv), aldehyde **6** (1 g, 1 equiv), and sulfone **3** (1.46 g, 1.3 equiv) in THF (37.5 mL) and DMF (12.5 mL) was heated at 70 °C 16 h. After cooling to room temperature, workup and purification similar to conditions A furnished **26** as white solid (920 mg, 93% yield). The analytical data were identical with those of an authentic sample.

Acknowledgment. Professor Fürstner is gratefully acknowledged for constant support and fruitful discussions.

Supporting Information Available: Procedures for the preparation of compounds **3**, **45**, and **52**−**54**; characterization data of all new compounds; copies of chiral GC spectra of compounds **38**−**40**; copies of NMR spectra of compounds **3**, **45**, **52**−**54**, and olefins of Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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